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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/670,105 | 09/26/2000 | Maurice Moncany | 2356.0062-05 | 5805 |

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| EXAMINER | |
|---|---|
| WINKLER, ULRIKE | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | Application No. | Applicant(s) | |
|---|---|---|---|
| **Office Action Summary** | 09/670,105 | MONCANY ET AL. | |
| | **Examiner** | **Art Unit** | |
| | Ulrike Winkler | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *27,28,32,33,38,39,43,44 and 49-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27, 28, 32, 33, 38, 39, 43, 44, 49-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The Amendment filed May 17, 2004 in response to the Office Action of November 17, 2003 is acknowledged and has been entered. Claims 27, 28, 32, 33, 38, 39, 43, 44, 49-64 and newly added claims 65-69 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

### *Claim Rejections - 35 USC § 112*

The rejection of claims 27, 28, 32, 33, 38, 39, 43, 44, 49-64 and newly added claims 65-69 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention **is maintained** for reason of record. The instant invention is drawn to polypeptide fragments of viral proteins, specifically viral Env proteins. The claimed polypeptides are described based on the method of obtaining the sequences of yet undiscovered and undisclosed polynucleotide sequences. Applicant's were in possession of the claimed sequences disclosed drawn to the specific viral strains disclosed in the specification HIV-1 Mal, HIV-1-Ely, HIV-1 Bru, HIV-2 Rod (CNCM No. I-522) and SIV1-lac (CNCM No. I-521). However, applicants were not in possession of yet undiscovered and mutated new viral strains as encompassed by the instant claims.

Applicant argues that it is proper to claim a compound using a product-by-process claim format. This may be true as long as the product-by-process results in the production of a defined

compound, in this instance applicants are amplifying a hypervariable domain whose structure is not known until after the amplification step is completed using oligonucleotide primers to regions that have a conserved structure. Applicant argues that the process steps recited in the pending claims help to provide the relevant information about the structural features of the claimed polypeptides, and thus the claim provides relevant identifying characteristics. The conserved structural regions do not provide any indications of the structure found in between the primer sites which is the composition being claimed in the instant invention. Applicant argues that the primers define the structural region of the amplified nucleic acids encoding the polypeptide. Applicant argues that the Office has overlooked the "identifying characteristics of the claimed polypeptides and instead focuses on the region of the polypeptide encoded by the portion of the amplified nucleic acid located between the primers.....in essence the office ignores the conserved sequences in the claimed polypeptide" (see response of May 17, 2004 at page 18). In this instance the method to obtain the product provides only the conserved structure at either end of the sequenced polynucleotide encoding the polypeptide. The method specifically focuses on obtaining the unknown sequences between the conserved structure and it is this structure that is claimed in the instant invetion.

The 3-D structure of a protein cannot be described merely by describing short evolutionarily conserved regions of the nucleic acid sequence that encodes the protein. The replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein [see *Burgess et al.* Journal of Cell Biology. (1990) Vol. 111, p 2129-2138]. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or

asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen [see *Lazar et al.* Molecular and Cellular Biology (1988) Vol. 8, No. 3, p 1247-1252 ]. Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies [see *Tao et al.* The Journal of Immunology (1989) Vol. 143 No. 8, p. 2595-2601]. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Changes in the amino acid sequence of the antigen can have a direct effect on the ability of the antibody to bind the protein, furthermore, the changes that effect the antibody binding do not have to occur within the epitope binding region [see *Abaza et al.* Journal of Protein Chemistry (1992) Vol. 11, No. 5, pages 433-444 and *Nuss et al.* Journal of Molecular Biology (1994) Vol. 235, pages 747-759] A single point mutation in the envelope of HIV alters the structure of the polypeptide to such a an extent that neutralizing antibody will no longer recognize the sequence [see *di Marzo et al.* Journal of Biological Chemistry (December 1993) Vol. 268, No. 34, pages 25894-25901]. Therefore, the art is replete with evidence that the whole protein structure or even a fragment of a protein structure can be structurally described by merely disclosing small portions of the protein that have been shown to be evolutionarily conserved when a single amino acid substitution can have a dramatic effect on the structure of the entire protein.

Applicants have been granted a patent to the oligonucleotide primers (U.S. Pat. No. 5,688,637) used in the instantly claimed product-by-process claims, in addition Applicants have also been granted a patent directed to the method of preparing a polypeptide using the

oligonucleotide primers (U.S. Pat. No. 5,786,177). In the instant invention Applicants are claiming a composition (products) that is made using the patented method of preparing the polypeptide. "Regardless of whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from noninfringing compounds, or infringing methods from non-infringing methods" see *University of Rochester v G.D. Searle & Co.*, 69, USPQ 2d 1886 (CA FC 2004) at 1894. Because one skilled in the art would conclude that the inventors were not in possession of the claimed polypeptides, the claims fail to comply with the written description requirement.

The rejection of claims 27, 28, 32, 33, 38, 39, 43, 44, 49-64 and newly added claims 65-69 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention **is maintained** for reason of record. The instant invention is drawn to polypeptide fragments of viral proteins, specifically viral Env proteins. The specific strains of viruses disclosed in the specification are HIV-1 Mal, HIV-1-Ely, HIV-1 Bru, HIV-2 Rod (CNCM No. I-522) and SIV1-lac (CNCM No. I-521). The claimed polypeptides are describes based on the method of obtaining the sequences of yet undiscovered and undisclosed polypeptides.

Applicant argues that the office has not provided any technical reasons for questioning why one of ordinary skill in the art could not make the claimed polypeptide using the process steps recited in the pending claims. That even in unpredictable arts, section 112, first paragraph

does not require disclosure of every species encompassed by the claims. Applicants have asserted that the Office has not provided any technical reasons or evidence or a Wands Factor analysis to support the enablement rejection.

Protein chemistry is probably one of the most unpredictable areas of biotechnology and the 3-D structure of a protein cannot be described merely by describing short evolutionarily conserved regions of the nucleic acid sequence that encodes the protein. The replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein [see *Burgess et al.* Journal of Cell Biology. (1990) Vol. 111, p 2129-2138]. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen [see *Lazar et al.* Molecular and Cellular Biology (1988) Vol. 8, No. 3, p 1247-1252 ]. Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies [see *Tao et al.* The Journal of Immunology (1989) Vol. 143 No. 8, p. 2595-2601]. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Changes in the amino acid sequence of the antigen can have a direct effect on the ability of the antibody to bind the protein, furthermore, the changes that effect the antibody binding do not have to occur within the epitope binding region [see *Abaza et al.* Journal of Protein Chemistry (1992) Vol. 11, No. 5, pages 433-444 and *Nuss et al.* Journal of Molecular Biology (1994) Vol. 235, pages 747-759] A single point mutation in

the envelope of HIV alters the structure of the polypeptide to such a an extent that neutralizing antibody will no longer recognize the sequence [see *di Marzo et al.* Journal of Biological Chemistry (December 1993) Vol. 268, No. 34, pages 25894-25901]. Therefore, the art is replete with evidence that the whole protein structure or even a fragment of a protein structure can be structurally described by merely disclosing small portions of the protein that have been shown to be evolutionarily conserved when a single amino acid substitution can have a dramatic effect on the structure of the entire protein.

"The only claims that appear to be supported by the specification are claims to assay methods, but those claims were already issued in the '497 patent" see *University of Rochester v G.D. Searle & Co.,* 69, USPQ 2d 1886 (CA FC 2004) at 1896. In this instance the specification provides a method of screening for nucleotide sequences that encode proteins, however, the specification does not disclose the structure of the proteins belonging to viral strains and mutants other than those five (HIV-1 Mal, HIV-1-Ely, HIV-1 Bru, HIV-2 Rod (CNCM No. I-522) and SIV1-lac (CNCM No. I-521)) disclosed in the specification without undue experimentation. Therefore, the instant invention is not enabled for the peptide fragments and the pharmaceutical compositions comprising the peptide fragments.

The rejection of claims 27, 28, 32, 33, 38, 39, 43, 44 and 49-64 recite limitations in the claims that have insufficient antecedent basis for the limitation in the claims. For example: the "a nucleotide sequence" followed by the limitation "the nucleic acid **is withdrawn** in view of Applicants amendment to the claim.

***Conclusion***

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 8/6/04